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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,165	11/14/2003	Stephen D. Gillies	LEX-004C1	2258

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EXAMINER	
TUNGATURTHI, PARITHOSH K	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 02/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/714,165	GILLIES, STEPHEN D.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-50* is/are pending in the application.

4a) Of the above claim(s) *50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8.6.04/4.8.04/7.19.05*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 28-49 in the reply filed on 12/15/05 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

2. Claims 1-27 have been cancelled.

3. Claim 50 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions. Applicant timely traversed the restriction (election) requirement in the reply on 3/24/05.

4. Claims 28-49 are under examination.

Specification

5. The first line of the specification does not indicate the status of the USSN 09/292,217, as abandoned. Appropriate correction is required.

NOTE: The variable region derived from mouse KS-1/4 antibody, which is reactive with the EpCAM antigen is described in Gillies et al (C) (U.S. Patent 6838260; Filed December 4, 2001 and claims priority to U.S. Ser. No. 08/986,997, filed on December 8th, 1997), and hence a deposit requirement is not required. The instant reference discloses the amino acid sequences for EpCAM and for mouse KS-1/4 antibody.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 28-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gillies (a) (WO 92/08495; International Publication Date: 29 May 1992) in view of Strom et al (WO 96/18412; International Publication Date: 20 June 1996) and in view of Armitage et al (J. Immunology 1995, 154:483-490) and in view of Gillies et al (b) (US Patent 5650150, Date Issues 07/22/1997) and in view of Gillies et al (c) (US 6838260; Filed 12/8/1997).

The instant claims are drawn to an immunoconjugate comprising an antibody binding site of an immunoglobulin (Ig) chain linked to an interleukin (1L)-15, wherein the antibody binding site is capable of binding a specific surface antigen present on a

preselected cell-type, wherein the preselected cell-type is a cancer cell or a virally-infected cell, wherein the cancer cell is in a solid tumor, wherein the antibody binding site is capable of binding an epithelial cell adhesion molecule (EpCAM), wherein the antibody binding site comprises a variable region derived from mouse KS-1/4 antibody, wherein the variable region is a humanized variable region, further comprising an immunoglobulin heavy chain constant region derived from an IgG1 heavy chain, 1gG2 heavy chain, IgG3 heavy chain, IgG4 heavy chain. The claims further recite an immunoconjugate comprising an antibody binding site of an immunoglobulin (Ig) chain linked to an interleukin (1L)-15, wherein the antibody-binding site comprises a portion of an immunoglobulin (1g) heavy chain, wherein the antibody binding site comprises an immunoglobulin variable region, further comprising an immunoglobulin constant region, wherein the immunoglobulin constant region comprises one or more of a CH1 domain, a CH2 domain, a CH3 domain or a CH4 domain, a CH1 and a CH2 domain, further comprising an immunoglobulin hinge region, wherein the immunoglobulin constant region is derived from an immunoglobulin chain selected from the group consisting of an IgG, IgM and 1gE chain, wherein the antibody binding site comprises a variable region of a heavy chain and a variable region of a light chain, further comprising a linker. The claims further recite expression vector encoding the immunoconjugate and a composition for administration to an animal comprising the immunoconjugate and a physiologically acceptable carrier or vehicle.

Gillies (a) teaches an immunoconjugate comprising an antibody having a specificity for a surface antigen on a targeted cell and a cytokine, said immunoconjugate retains the antigen binding activity of the immunoglobulin and the biological activity of the cytokine and can be used to specifically deliver the cytokine to the target cell (page 4 first paragraph, in particular). The immunoconjugate taught by Gillies (a) comprises a cytokine and an immunoglobulin variable region which is derived from an antibody specific for the target antigen and constant regions which include CH1, CH2 and CH3 domains, (page 11 last paragraph, in particular). In addition, Gillies (a) teach that the gene encoding the cytokine is joined, e.g., by appropriate linkers, e.g., by DNA encoding $(Gly_4\text{-}Ser)_3$ in frame to the 3' end of the gene encoding the constant region (e.g., CH3 exon), either directly or through an intergenic region (page 11, last paragraph, in particular). The immunoconjugate taught by Gillies (a) is produced by constructing a gene construct in a 5' to 3' orientation which comprises a DNA segment encoding a heavy variable chain, a DNA segment encoding the heavy chain constant region and a DNA coding for the cytokine (page 10 third paragraph, in particular). The immunoconjugate taught by Gillies (a) is used to deliver selectively a cytokine to a target cell in vivo so that the cytokine can exert a localized biological effect such as a local inflammatory response or antibody-dependent cellular cytotoxicity (ADCC), and can be used in a method of treating cancer by targeted lysis, (page 14 third paragraph and bottom of page 6, in particular).

However, Gillies (a) does not teach an immunoconjugate comprising an antibody binding site of an immunoglobulin (Ig) chain linked to an interleukin (1L)-15, wherein the

antibody binding site is capable of binding an epithelial cell adhesion molecule (EpCAM), wherein the antibody binding site comprises a variable region derived from mouse KS-1/4 antibody, wherein the variable region is a humanized variable region, wherein the antibody-binding site comprises an immunoglobulin (Ig) heavy chain, wherein the antibody binding site comprises an immunoglobulin variable region, further comprising an immunoglobulin hinge region, wherein the immunoglobulin constant region is derived from an immunoglobulin chain selected from the group consisting of an IgG, IgM or 1gE chain, wherein the antibody binding site comprises a variable region of a heavy chain and a variable region of a light chain. These deficiencies are made up for by Strom et al, Armitage et al, Gillies et al (b) and Gillies et al (c).

Strom et al teach chimeric proteins which include a cytokine and an enzymatically inactive polypeptide, and therapeutic uses thereof (abstract, in particular), Strom et al teach that the enzymatically inactive peptide can include an IgG hinge region and a half-life increasing polypeptide such that the IgG hinge region is bonded to the cytokine and serves as a flexible polypeptide spacer between the cytokine and the half-life-increasing polypeptide, wherein the half-life-increasing polypeptide can be IgG Fc (page 9 lines 4-9, in particular). Strom et al also teach that the cytokine portion of the chimeric protein can be an interleukin, such as IL-15 (page 9 lines 21-25 and claim 14 in particular).

Armitage et al teach (please see introduction and discussion, in particular) that the cytokine IL-15 shares several T cell-stimulatory properties with IL-2, including the ability to costimulate proliferation of primary T cells and the murine CTLL line and to

induce the generation of CTL and lymphokines-activated killer cells. Armitage et al also teach that IL-15 and IL-2 have comparable activity on B cells, both cytokines being able to induce proliferation of purified B cells costimulated with anti-IgM or phorbol ester. Armitage et al futher teach that IL-15 induces proliferation of activate, but not resting, B cells and induces secretion of IgM, IgG and IgA in combination with recombinant CD40L, in addition to that only IL-15 can replace IL-2 for the generation of Ag-specific primary responses in vitro. Armitage et al also teach (entire document and the references cited) that in contrast to IL-2, IL-15 manifests anti-apoptotic actions, inhibits IL-2-mediated AICD and stimulates the persistence of $CD8^+$ memory cells and also that in light of such valuable characteristics, IL-15 may be superior to IL-2 in the treatment of cancer and especially as a component of vaccines where a prolonged immune response is desirable.

Gillies et al (b) teach immunoconjugate for the selective delivery of a cytokine to a target cell (Abstract in particular). Gillies et al (b) teach the fusion proteins comprised of an immunoglobulin heavy chain having a specificity for the target cell, such as a cancer or virus-infected cell, and a cytokine, such as lymphotoxin, tumor necrosis factor alpha, interleukin-2, or granulocyte-macrophage colony stimulating factor, joined via its amino terminal amino acid to the carboxy-terminus of the immunoglobulin. Gillies et al (b) also teach nucleic acid sequences encoding these fusion proteins and methods of their preparation by genetic engineering techniques. Gillies et al (b) also teach that the immunoconjugate of the invention includes a variable region and a constant region which may be the constant region normally associated with the variable region, or a

different one and thus a V/C chimera; e.g., variable and constant regions from different naturally occurring antibody molecules or from different species. Gillies et al (b) further teach that the chimeric Ig chain comprises a heavy (H) chain which includes the CH1, CH2 and CH3 domains (paragraph 14, in particular) and that the heavy chain constant region for the conjugates can be selected from any of the five isotypes: alpha, delta, epsilon, gamma or mu heavy chains or various subclasses (such as the IgG subclasses 1-4) can be used. Gillies et al (b) also teach the immunoconjugate wherein the variable region is a mouse Ig variable region and the CH1 and CH2 domains are human Ig CH1 and CH2 domains (claim 4, in particular).

Gillies et al (C) teach an antibody-IL-12 fusion protein wherein the antibody is KS-1/4, reactive with the EpCAM antigen, and the treatment of established colon carcinoma with antibody-IL-12 fusion protein (example 7, in particular).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced an immunoconjugate comprising an antibody binding site of an immunoglobulin (Ig) chain linked to an interleukin (1L)-15 further comprising all the limitations as claimed.

One of ordinary skill in the art would have been motivated and would have reasonable expectation of success to have produced an immunoconjugate comprising an antibody binding site of an immunoglobulin (Ig) chain linked to an interleukin, wherein the antibody binding site is capable of binding a specific surface antigen

present on a preselected cell-type, wherein the preselected cell-type is a cancer cell or a virally-infected cell as taught by Gillies (a), because Gillies (a) teaches an immunoconjugate comprising an antibody having a specificity for a surface antigen on a targeted cell and a cytokine, said immunoconjugate retains the antigen binding activity of the immunoglobulin and the biological activity of the cytokine and can be used to specifically deliver the cytokine to the target cell, and further the immunoconjugate taught by Gillies (a) is used to deliver selectively a cytokine to a target cell in vivo so that the cytokine can exert a localized biological effect such as a local inflammatory response or antibody-dependent cellular cytotoxicity (ADCC), and can be used in a method of treating cancer by targeted lysis.

In addition, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have combined the teachings of Gillies (a) with Strom et al and Armitage et al, because Gillies (a) teach an immunoconjugate comprising an antibody having a specificity for a surface antigen on a targeted cell and a cytokine and because Strom et al teach chimeric proteins which include a cytokine and an enzymatically inactive polypeptide, and therapeutic uses thereof, wherein the enzymatically inactive peptide can include an IgG hinge region and a half-life increasing polypeptide, wherein the half-life-increasing polypeptide can be IgG Fc in addition to teaching that the cytokine portion of the chimeric protein can be an interleukin, such as IL-15; and because Armitage et al teach that the cytokine IL-15 shares several T cell-stimulatory properties with IL-2, including the ability to costimulate proliferation of primary T cells and the murine CTLL line and to induce the generation of

CTL and lymphokines-activated killer cells, in addition to inducing proliferation of purified B cells costimulated with anti-IgM or phorbol ester, and that only IL-15 can replace IL-2 for the generation of Ag-specific primary responses in vitro.

Moreover, one of ordinary skill in the art would have known to combine the teachings of Gillies (a) and Strom et al with the teachings of Gillies (b) and Gillies (c), because Gillies (a) teach an immunoconjugate comprising a cytokine and an immunoglobulin variable region which is derived from an antibody specific for the target antigen and constant regions which include CH1, CH2 and CH3 domains, in addition to that the gene encoding the cytokine is joined, e.g., by appropriate linkers, e.g., by DNA encoding $(Gly_4\text{-}Ser)_3$ in frame to the 3' end of the gene encoding the constant region (e.g., CH3 exon) and because Strom et al teach a chimeric protein which include a cytokine and an IgG Fc and because Gillies et al (b) teach the fusion proteins comprised of an immunoglobulin heavy chain having a specificity for the target cell, such as a cancer or virus-infected cell, and a cytokine, such as lymphotoxin, tumor necrosis factor alpha, interleukin-2, or granulocyte-macrophage colony stimulating factor, in addition to teaching that the immunoconjugate of the invention includes a variable region and a constant region which may be the constant region normally associated with the variable region, or a different one and thus a V/C chimera; e.g., variable and constant regions from different naturally occurring antibody molecules or from different species; and further teach the immunoconjugate wherein the variable region is a mouse Ig variable region and the CH1 and CH2 domains are human Ig CH1 and CH2 domains (claim 4, in particular).

Furthermore, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have generated the immunoconjugate as claimed and expression vector encoding the immunoconjugate and a composition for administration to an animal comprising the immunoconjugate and a physiologically acceptable carrier or vehicle because Gillies (a) teaches an immunoconjugate comprising an antibody having a specificity for a surface antigen on a targeted cell and a cytokine, and because Strom et al teach a chimeric protein which include a cytokine (IL-15) and an IgG Fc, and because Gillies et al (b) teach the fusion proteins comprised of an immunoglobulin heavy chain having a specificity for the target cell in addition to teaching the nucleic acid sequences encoding these fusion proteins and methods of their preparation by genetic engineering techniques and because Gillies et al (C) teach an antibody-IL-12 fusion protein wherein the antibody is KS-1/4, reactive with the EpCAM antigen, and the treatment of established colon carcinoma with antibody-IL-12 fusion protein and because Armitage et al also teach that IL-15 manifests anti-apoptotic actions, stimulates the persistence of $CD8^+$ memory cells and also that IL-15 may be useful in the treatment of cancer and especially as a component of vaccines where a prolonged immune response is desirable.

Thus it would have been obvious to one skilled in the art to have produced an immunoconjugate comprising an antibody binding site of an immunoglobulin (Ig) chain linked to an interleukin (1L)-15 further comprising all the limitations as claimed.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

8. No claims are allowed

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

10. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
Parithosh K. Tungaturthi, Ph.D.
Ph: (571) 272-8789

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER